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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/658,856	09/09/2003	Gary R. Grotendorst	FIBRO1130-3	3430

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EXAMINER	
SPECTOR, LORRAINE	

ART UNIT	PAPER NUMBER
1647	

MAIL DATE	DELIVERY MODE
06/04/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/658,856	GROTENDORST ET AL.	
	Examiner	Art Unit	
	Lorraine Spector, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15,19-23 and 37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15,19-23 and 37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 15, 19-23 and 37 are pending and under consideration.

Specification

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Applicants did not respond to this requirement in the amendments filed 4/9/2007 or 1/9/2008. Further failure to address this issue will result in the response being found non-responsive.

Claim Interpretation

It is noted that the claims as amended are drawn to antibodies that bind to C-terminal fragments of CTGF "consisting of" specified residues, that represent exons IV and V of the full-length protein.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 15, 19-23 and 37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 15 recites that residues 4-74 of SEQ ID NO: 4 constitute a C-terminal fragment of CTGF. This is not correct, and therefore indefinite. Residue 74 of SEQ ID NO: 4 is actually 98 residues from the C-terminus of the protein.

The remaining claims are rejected for depending from an indefinite claim.

Rejections over Prior Art

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (f) he did not himself invent the subject matter sought to be patented.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 15, 19, 21-23 and 37 under 35 U.S.C. §103 as being obvious over Grotendorst et al., U.S. Patent Number 5,408,040, cited by applicants. Whereas Grotendorst and Neff are the inventors of the instant application, the patent names Grotendorst and Bradham, Jr. as inventors. Grotendorst et al. teaches antibodies which specifically bind to CTGF, but not to PDGF; see claims 2-4. The antibodies may also be monoclonal or polyclonal. At column 5, lines 37-45, it is disclosed that antigenic fragments may be used to make antibodies. At column 6 Grotendorst teaches pharmaceutical uses for the antibodies for treating humans, thus anticipating claim 23 (see lines 16-22), radiolabeled antibodies (lines 34-35) and functional fragments of the antibodies (lines 47-50). At column 7, it is disclosed that goat antibodies were made to synthetic peptides containing the carboxyl sequences of the PDGF protein (as pointed out by applicants), which antibodies bound to CTGF; this is how CTGF was first isolated. The carboxyl terminus of SEQ ID NO: 4 corresponds to the carboxyl terminus of PDGF.

Paragraph DETX(19) of the '040 patent states:

> The invention provides antibodies which are specifically reactive with CTGF polypeptide or fragments thereof. Although this polypeptide is cross reactive with antibodies to PDGF, not all antibodies to CTGF will also be reactive with PDGF. Antibody which consists essentially of pooled monoclonal antibodies with different epitopic specificities, as well as distinct monoclonal antibody preparations are provided.

> Monoclonal antibodies are made from antigen containing fragments of the protein by methods well known in the art (Kohler, et al., Nature, 256:495, 1975; Current Protocols in Molecular Biology, Ausubel, et al., ed., 1989). *Monoclonal antibodies specific for CTGF can be selected, for example, by screening for hybridoma culture supernatants which react with CTGF, but do not react with PDGF. (Emphasis added.)*

This, taken with the previously cited teachings of making antibodies to the terminal portions of PDGF, fairly puts into the hands of the public antibodies that bind to the C-terminus of CTGF, compositons thereof, and methods of using such. Thus, the '408 patent puts into the hands of the public antibodies to the C-terminus of CTGF, via it's teachings of making monoclonal and polyclonal antibodies to CTGF, and the teaching of making antibodies to synthetic peptide fragments of PDGF, a clearly analogous protein. It is noted that applicants have added the limitation to claim 15 that the antibodies not bind PDGF; this limitation is clearly taught by Grotendorst et al., as shown in the above quotation.

With reagard to the limitation that the claimed antibodies inhibit DNA replication, the specification teaches at column 2 that "the primary biological activity of CTGF polypeptidee is its mitogenicity, or ability to stimulate target cells to proliferate." As proliferation requires DNA synthesis, this clearly teaches that CTGF stimulates such, either directly or indirectely. Thus, this property is inherent to some or all of the claimed antibodies. Accordingly, when one combines the teaching of using antibodies that inhibit the mitogenic ability of CTGF, which would also inhibit DNA synthesis, antibodies that have that property are obvious over Grotendorst. It has long been established that screening antibodies for a particular property does not constitute undue experimentation; see *Hybritech inc. v. Monoclonal Antibodies, Inc. 802 F2d 1367, 1986 is withdrawn in view of applicants arguments and/or amendments.* states:

> With respect to screening, the only permissible view of the evidence is that screening methods used to identify the necessary characteristics, including affinity, of the monoclonal antibodies used in the invention were known in the art and that the '110 patent contemplated one of those. At trial, Monoclonal's counsel stated "it is a procedure that was known in '78." In similar fashion, the district court held that the claimed subject matter would have been obvious in part because the "existence of monoclonal antibodies *having the affinity constants claimed in the patent was well known* prior to the alleged invention . . . ." [Emphasis ours.] Furthermore, there was not a shred of evidence that undue experimentation was required by those skilled in the art to practice the invention. We hold as a matter of law that the '110 patent disclosure is enabling.

The Examiner's position is also supported by the recent finding by the Supreme Court in *KSR v. Teleflex, Inc.* (82 USPQ 2d 1385, 4/30/2007), which held that "a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103." (See 82 USPQ2d at 1397.) In this case, the reference teaches making antibodies to inhibit the mitogenic activity of CTGF.

Applicants argue that the properties of the claimed antibodies are not taught by the '408 patent; this is not persuasive: See In re Graves, 36 USPQ 2d1697 at 1701, which teaches that A reference anticipates a claim if it discloses the claimed invention "such that a skilled artisan could take its teachings in combination with his own knowledge of the particular art and be in possession of the invention" such is the case with the '408 patent.

In the response filed 1/9/2008, applicants argue at page 8 that Grotendorst does not specifically teach antibodies to exons 4 and 5 of the protein, but rather to "the entire C-terminal region of PDGF". As applied to CTGF, the subject matter of the claims encompasses antibodies to residues 4 through 172 of SEQ ID NO: 4. CTGF is 349 residues in length. The first 26 residues are a signal sequence, and would not appear in the mature protein. Accordingly, the mature protein is 343 residues long. Thus, the 172 residues of the claim constitute exactly 50% of the mature protein. Thus, regardless of the lack of teaching by the reference of particular exons, applicants are claiming antibodies to the entire C-terminal portion of the protein. As stated above, in view the teachings of Grotendorst et al., it would have been obvious to obtain antibodies that inhibited DNA replication. The fact that those antibodies would have bound to the C-terminus of CTGF would have been inherent, in the express absence of evidence to the contrary.

Accordingly, the claims are obvious over Grotendorst et al.

Claim Rejections - 35 USC § 103

Claim 20 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Grotendorst et al. in view of Hoogenboom et al., U.S. Patent No.5,565,332.

The teachings of Grotendorst et al. are summarized above. Grotendorst does not specifically teach human antibodies.

Hoogenboom et al. disclose human and humanized antibodies and methods of making such. At col. 1 lines 16-30 they disclose the advantages of such as being overcoming the problem of elicitation of anti-globulin response when a non-human antibody is administered to a human. See also col. 3 lines 8-15 in this regard. At col. 2 lines 57+, they disclose that antibody fragments can perform the function of whole antibodies, and set forth single chain antibodies as being examples of antibody fragments.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to substitute the anti-CTGF antibodies of Grotendorst into the human or humanized antibodies of Hoogenboom et al. to attain the known and expected advantages of such as set forth by the secondary reference and as discussed above.

Applicants traversal of this rejection has been fully considered but is not deemed persuasive for reasons cited with regard to the rejection under 35 U.S.C. §102(b). In addition, applicants argue that there was no motivation to combine the references. This argument has been fully considered but is not deemed persuasive. The specificaton teaches that :

"Therapeutically, antibodies or fragments of the antibody molecule could also be used to neutralize the biological activity of CTGF in diseases where CTGF is inducing the overgrowth of tissue." (See col. 2, lines 45-52.)

Given the disclosure of Grotendorst of the properties of CTGF and the suggestion that antibodies thereto be used in clinical application, there is ample motivation to make humanized antibodies as taught by Hoogenboom.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 15, 19, 21-23 and 37 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 2-4 of U.S. Patent No. 5,408,040. Although the conflicting claims are not identical, they are not patentably distinct from each other for reasons cited in the above rejection under 35 U.S.C. §102(b) and (f).

Claim 20 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 2-4 of U.S. Patent No. 5,408,040 in view of Hoogenboom et al., U.S. Patent No. 5,565,332. for reasons cited above.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Tamatani et al, U.S. Patent No.6,562,618, disclose and claim anti-CTGF antibodies. The foreign priority date for the patent is 12/15/1998, one day after the claimed priority for this application.

These rejections are maintained for reasons of record.

No claim is allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 3:00 P.M. at telephone number 571-272-0893.

If attempts to reach the Examiner by telephone are unsuccessful, please contact the Examiner's supervisor, Dr. Manjunath Rao, at telephone number 571-272-0939.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to **571-273-8300**. Faxed draft or informal communications with the examiner should be directed to ***571-273-0893.***

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Lorraine Spector/ , Ph.D.
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